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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,542	01/16/2002	Wilfred Arthur Jefferies	7685-41	3450

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/046,542	JEFFERIES ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-12, and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 4/21/05 has been entered. Claims 2 and 13 have been canceled. Claims 1, 3-12, and 14-20 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action. Further, please note that while the examiner of record remains the same, the art unit number has changed from 1632 to 1633.

Restriction/Election

The applicant has canceled claims 2 and 13 and amended claim 1 to reflect the elected subject matter, i.e. wherein the agent is a nucleic acid sequence comprising a sequence encoding a TAP molecule. The applicant, however, states that they reserve the right to reintroduce the subject matter of canceled claim 13, which was drawn to non-elected subject matter, at a later date upon allowance of the linking claim, claim 1. In response, however, the applicant is reminded that only claim(s) directed to the nonelected invention(s), previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim can be rejoined and examined for patentability, see MPEP 809. In this case, claim 1 has been amended such that it is no longer a linking claim. Claim 1 is now directed to the elected

invention. As such, if claim 1, as amended, is found allowable, claim 13 cannot be rejoined, since an allowable linking claim would not be present in the application.

Double Patenting

The rejection of pending claims 1, 4-5, 7, 9, and 14-19 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,361,770 B1 (3/26/02), hereafter referred to as the '770 patent, is maintained as the applicants have not traversed the grounds of rejection. However, it is noted that the applicant has stated their intention to file a terminal disclaimer upon indication of allowable claims.

Claim Rejections - 35 USC 112

The rejection of pending claims 1, 3-12, and 14-20 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the specification provides sufficient evidence that adminsitering a TAP molecule can enhance an immune response to many different types of antigens and that case law does not require them to disclose or test every possible antigen. In response, the rejection of record presented a detailed analysis of the working examples provided in the instant specification and a detailed analysis of the state of the art of TAP transporters and their ability to

enhance immune responses and identified the following enabled subject matter: 1) methods of augmenting a CTL response in a mammal to tumor cells expressing low or nondetectable levels of peptide/MHC class I complexes on the cell surface comprising ex-vivo introduction of a nucleic acid encoding TAP-1 into the tumor cells followed by introduction of the tumor cell into the mammal, 2) methods of augmenting a CTL response in a mammal to a tumor cell expressing low or nondetectable levels of peptide/MHC class I on the cell surface comprising introducing a vaccinia virus encoding TAP-1 into the tumor cell, and 3) in-vitro methods of enhancing a CTL response to VSV antigens in a cell expressing low or nondetectable levels of peptide/MHC I on the cell surface comprising, introducing into said cell a nucleic acid comprising a sequence encoding TAP-1 or TAP-2. Applicant's response does not address any of the specific evidence for non-enablement of the full scope of the claims as written provided in the previous office action. Rather, the applicant simply refers the examiner to the working examples and specification. The relevant sections of the previous office action which discuss the disclosure provided in the specification and the working examples in particular is reiterated below for applicant's convenience.

The specification discloses the transfection of cells, preferably tumor cells, that have low to undetectable levels of TAP-1 and TAP-2, and low levels of MHC class I on the cell surface, with either TAP-1 or the TAP-2 resulting in increased surface expression of endogenous peptide/MHC class I complexes on the cell surface. The specification further discloses that the target cells transfected with TAP-1 or TAP-2 will express enhanced levels of peptide/MHC leading to an enhanced immune surveillance of the peptides in the host. In addition, the specification discloses said method wherein the target cell additionally has a deficiency in

proteasome components, where TAP-1 or TAP-2 is introduced into the cell as a viral vector, and wherein the endogenous peptide is a viral or tumor antigen.

At the time of filing, the skilled artisan did not consider the transfection of either TAP-1 or TAP-2 alone into cells expressing little to no TAP-1 and TAP-2 as sufficient to enhance or increase presentation of endogenous peptide/MHC class I on the cell surface. Several independent researchers at the time of filing had demonstrated that transfection of TAP-1 or TAP-2 alone into TAP-1/TAP-2 negative cells neither increased the level of MHC class I expression on the cell surface nor resulted in increased peptide specific CTL lysis. Spies et al. transfected 721.174 cells, which have a deletion in both TAP genes, with TAP-1 (PSF-1) and showed that TAP-1 alone was incapable of increasing surface expression of MHC class I (Spies et al., (1991) Nature, Vol. 351, page 323, abstract and Figure 1). Whereas Spies et al. looked at presentation of endogenous self-antigens, Momberg et al. demonstrated that T-2 cells, which are also TAP-1/TAP-2 negative, required transfection of both TAP-1 and TAP-2 in order to present endogenous viral antigens derived from Influenza virus in the context of MHC class I for surface expression and CTL recognition and lysis (Momberg et al. (1992) Nature, Vol. 360, page 174, Tables 1+2, and page 175, Figure 1). As Povis et al. states, A ...the integrity of both transporter polypeptides is required for any significant class I membrane expression or cytosolic peptide presentation. This conclusion is consistent with a model in which the two transporter polypeptides are required to associate in order to form a functional heterodimer A (Povis et al., (1991), Nature, Vol. 354, page 531, paragraph 2). Thus, in view of the state of the art at the time of filing, the artisan would not have predicted that MHC class I expression and CTL specific

lysis of target cells could be increased by the transfection of any TAP-1/TAP-2 negative cells line with either TAP-1 or TAP-2 alone.

Regarding the enhancement of anti-viral immune responses, the applicant provides several *in vitro* working examples of the instant invention regarding the enhancement of viral peptide specific CTL responses with TAP molecules. *In vivo* examples involving viral peptide presentation are not provided. RMA-S cells, which have mutation in TAP-2, and CMT.64 cells, which the applicant demonstrates are deficient in TAP-1, TAP-2, and the proteasome components LMP-2 and 7, are used in the *in vitro* working examples. The applicant first demonstrates that untransfected RMA-S cells do not require TAP-2 in order to effectively present VSV derived peptides in the context of MHC class I on the cell surface as measured by VSV specific CTL lysis of VSV infected RMA-S cells. CMT.64 cells, however, which are deficient in both TAP-1 and TAP-2, are unable to present VSV peptide/MHC class I on the cell surface without γ-IFN treatment. The applicant goes on to show that CMT.64 cells transfected with TAP-1 and infected with VSV have increased surface expression of peptide bound MHC class I on the cell surface as measured by FACS analysis, and that CMT.64 cells transfected with either TAP-1 or TAP-2 can be recognized and lysed by VSV specific CTL. However, TAP-2 transfected CMT.64 cells show approximately half the amount of specific lysis than TAP-1 transfected cells, and neither TAP-1 nor TAP-2 transfected cells are lysed as efficiently as untransfected CMT.64 cells loaded with exogenous VSV peptide. However, the working examples further demonstrate that CMT.64 transfected with TAP-1 and infected with Influenza are **not** lysed by Influenza specific CTL suggesting that TAP-1 is *not* sufficient to allow processing and presentation of endogenous Influenza peptides in CMT.64 cells (specification ,

page 36, lines 9-15). Finally, the applicant's working example using HSV infected CMT.64 cells shows that HSV peptides are processed and presented independent of TAP-1 and TAP-2 as untransfected CMT.64 cells infected with HSV are lysed with equal efficiency as TAP-1 transfected CMT.64 (specification, page 36, lines 35-38). Viewed as a whole, the applicant's *in vitro* working examples demonstrate that of the viral antigens tested, **only** VSV peptides are capable of being processed, presented, and expressed on the cell surface of CMT.64 cells in the context of MHC class I following transfection of the cells with TAP-1 or TAP-2 and recognized by viral specific CTL. Therefore, based on the stated of the art of enhancing immune responses by introducing TAP molecules, the breadth of the claims, and the working examples which show that transfection of the CMT.64 cells with either TAP-1 or TAP-2 did not enhance Influenza peptide presentation and recognition by CTL, and HSV peptides are presented independent of TAP expression, the skilled artisan would not have been able to predict in the absence of undue experimentation whether the MHC class I presentation of any viral peptides other than VSV peptides could be enhanced by the transfection of TAP-1 or TAP-2 alone in cells which lack expression of both TAP-1 and TAP-2.

Thus, while the applicant's claims read on enhancing immune responses to any viral antigen by transfecting cells with a single TAP molecule, the specification shows that of 3 viral antigens tested, antigens derived from HSV are TAP independent such that TAP expression did not enhance immune responses, immune responses to antigens derived from Influenza virus require the expression of both TAP 1 and TAP 2, and only immune responses to antigens from VSV can be enhanced by the expression of TAP1 alone. As such, only 1 of 3 viral antigens tested worked in applicant's methods. Thus, in view of the teaching in the prior art that both TAP

molecules are required for enhanced immune presentation and responses to viral antigens, and applicant's own data which shows that immune responses could be enhanced to only 1 of 3 viral antigens tested, it would have required undue experimentation to practice the scope of the invention as claimed.

In support of the enhancement of presentation of endogenous tumor antigens and enhancement of anti-tumor immune responses, the applicant has provided several working examples which demonstrate that the transfection of tumor cells with low or nondetectable levels of peptide/MHC class I complexes on the cell surface either ex vivo with TAP-1 nucleic acid or in vivo with vaccinia virus encoding TAP-1 enhances surface expression of peptide/MHC class I complexes and enhances tumor specific CTL responses. However, the working examples provided also clearly demonstrate that transfection with TAP-2 alone is not effective, see examples 21 and 22, particularly page 74. Thus, in view of the high degree of unpredictability in art at the time of filing for generating anti-tumor immune responses by transfecting MHC class I low/negative cells with TAP-1 or TAP-2 alone, and applicant's data which demonstrates that while TAP-1 transfection can increase anti-tumor CTL responses TAP-2 transfection cannot, the skilled artisan would not have been able to predict without undue experimentation whether transfection of TAP-2 alone into any tumor type would be capable of enhancing any type of anti-tumor immune response.

In addition, the specification's working examples are limited to the direct administration of recombinant vaccinia virus encoding TAP-1 at or near the site of a tumor. The specification does not provide working examples demonstrating the use of other types of plasmid or viral vectors *in vivo* or other routes of delivery of TAP-1 to tumor cells other than delivery to the site

of the tumor in the mammal. The specification also fails to provide sufficient guidance for using vectors other than vaccinia virus to deliver TAP-1 to tumor cells or any other type of cell *in vivo*. In particular, the specification does not provide sufficient guidance concerning dosages and routes of *in vivo* delivery for any and all vectors which encode TAP-1, such as retrovirus, adenovirus, or plasmid vectors, wherein an enhanced anti-tumor immune response is observed. The art of time of filing considered the targeted *in vivo* delivery of recombinant vectors, and the expression of therapeutic levels of the encoded transgenes in the target cells as unpredictable. Verma et al. teaches that, "... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). Miller et al. supplements Verma et al. by teaching that successful gene therapy requires the delivery of the gene to the appropriate cell both efficiently and accurately and states that currently, "..improvements to the accuracy of a vector often compromise its efficiency, and vice versa" (Miller et al. (1995) FASEB, Vol. 9, page 190, columns 1-2 bridging paragraph). The specification does not teach strategies to target vector to tumor cells *in vivo* other than by direct, localized injection of the vector into the tumor itself.

In addition, the art at the time of filing did not consider gene therapy of cancer, particularly human cancer, using transduced or transfected tumor cells as predictable. Orkin et al. identifies several strategies for increasing anti-tumor immune responses including, " the transfer of genes for ... immunomodulatory products to cancer cells", either *ex vivo* or *in vivo*, " in an attempt to stimulate immune recognition of not only the gene modified cancer cells, but

also cancer cells that have not received the gene." , and concludes that, " [a]lthough several of these strategies show promise in mouse models, none has demonstrated efficacy in humans" (Orkin et al. (1995) "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", page 6, paragraph 5).

Thus, based on the unpredictable effects of gene delivery using both viral and non-viral vectors as taught by the art at the time of filing, and the lack of guidance provided by the specification for the use of any and all vectors and routes of *in vivo* vector delivery other than the direct administration of vaccinia virus encoding TAP-1 to the tumor site, it would have required undue experimentation for the skilled artisan to practice the instant invention as claimed. The applicant's argument that one skilled in the art could readily administer TAP molecules using other vectors and modes of administration is contradicted by the teachings of Verma et al., Miller et al., and Orkin et al.

Regarding the lack of enablement for genes inducible by tapasin, the applicant argues that tapasin was known in the art, one could readily identify tapasin inducible genes. In response, the specification fails to provide any description or enabling disclosure for a "gene inducible by tapasin". While the applicant's claims encompass potentially large number of nucleotide sequences, the instant specification fails to teach any gene which is inducible by tapasin or the nucleic acid sequence corresponding to any such gene. The specification further fails to provide any description of the particular physical, chemical, and biological features of a gene which is inducible by tapasin such that nucleic acid sequences corresponding to such genes could be identified. As such, the skilled artisan would not have been able to identify or use any "gene inducible by tapasin" without undue experimentation. Further, as genes inducible by tapasin are

not reported in the prior art, it is not predictable without undue experimentation whether such genes even exist.

Thus, for the reasons discussed in detail above, the rejection of record is maintained.

The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The rejection of record states that the specification fails to provide adequate written description for any gene which is inducible by tapasin. The applicant argues that the molecules listed in claim 10 are known molecules and that one of skill in the art could readily determine whether or not a gene is inducible by tapasin. In response, the rejection of record is only directed to a lack of written description for "genes inducible by tapasin". The written description of the other molecules listed in claim 10 is not at issue. Further, there is no evidence of record that "genes inducible by tapasin" were known in the art or even exist. As noted in the previous office action, the specification is completely silent as to the identity of these genes or as to the requisite structural or functional properties of such genes such that the artisan could recognize that the applicant was in possession of the invention as claimed. To say that such genes could be identified is not evidence of possession. As noted in the previous office action, case law states, "simply describing large genus of compounds is not sufficient to satisfy written description

requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification in the instant application does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of any gene which is inducible by tapasin, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids or the primers or probes needed for detection of such genes in any organism. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for genes inducible by tapasin.

The rejection of pending claims 1, 3-12 and 14-20 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC 102

The rejection of claims 1-5, 7-8, 16, and 19 under 35 U.S.C. 102(b) as being anticipated by Spies et al. (1992) Nature, Vol. 355, 644-646, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed below.

The applicant argues that Spies teaches away from the instant invention because Spies teaches that TAP-1 alone was incapable of increasing surface expression of MHC class I in cells with deletion in both TAP genes. In response, Spies, published in Nature in 1992, sets forth the results from experiments conducted a cell line, LCL .134, in which only the TAP-1 gene is missing. Spies et al. teaches enhancement of CTL response against an LCL mutant .134, in which the TAP-1 gene is missing, but TAP-2 is present, following the co-administration of a vaccinia virus encoding a viral antigen and plasmid vector encoding TAP-1 to the cells *in vitro* (Spies et al., pages 644-645, especially Figure 1). This is the teaching that anticipates the claims as written. The teachings of Spies cited by the examiner in the enablement rejection under 35 U.S.C. 112, first paragraph, references an earlier paper by Spies published in Nature in 1991. In this paper, Spies conducted experiments in **two different cell lines**, the same .134 cell line discussed in the later paper, which lack TAP-1 only, and a second cell line, .174, which lack **both** the TAP genes. In the 1991 paper, Spies teaches that expression of TAP-1 alone in the transfected LCL mutant .174 , in which both of the TAP genes are missing, is incapable of increasing surface expression of MHC class I. This teaching in no way contradicts or teaches away from the teachings of Spies regarding the other cell line, which only lacks TAP-1 expression. Therefore, applicant's arguments are not persuasive since the claims as written are broad and encompass the expression of TAP -1 in any cell type.

The rejection of claims 1-4, 6,-8, 16, and 19 under 35 U.S.C. 102(b) as being anticipated by Powis et al. (1991) Nature, Vol. 354, 528-531, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed below.

The applicant argues that Powis et al. teaches away from the instant invention because Powis teaches that the integrity of both transporter polypeptides is required for any significant class I membrane expression. In response, Powis et al. teaches the enhancement of CTL response against a mutant tumor cell, the RMA-S cell line which lacks functional expression of TAP-2, following the co-administration of influenza virus, which encodes influenza viral antigens, and a plasmid vector encoding TAP-2 to the cells *in vitro* (Powis et al., page 531, Figure 4). The fact that RMA-S cells express TAP-1 and yet lack surface class I expression, and the fact that expression of TAP-2 in these cells restored surface class I expression, led the authors to conclude that both transporter peptides, TAP-1 and TAP-2, are required for surface class I expression. Thus, there is no contradictory teachings in Powis. Further, the examiner has not been inconsistent in citing Powis as evidence of both anticipation and non-enablement because the claims as written are broad and read on the expression of TAP-2 in any type of cell. Powis teaches that while the expression of TAP-2 in cells which already express TAP-1 and which have a defect in TAP-2 can enhance immune responses, the expression of a single TAP 1 or TAP 2 gene in the absence of the other does not. Thus, applicants arguments are not persuasive.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER